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The Effects of Marihuana Extract Distillate on Eating Behavior of Rats

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AN ABSTRACT OF THE THESIS OF Terrie Wetle for the Master of Science
in Psychology presented June 30, 1971.

Title: The Effects of Marihuana Extract Distillate on
Eating Behavior of Rats.

APPROVED BY MEMBERS OF THE THESIS COMMITTEE:


Cord B. Sengstacke, Ph.D., Chairman


Robert Jones, Jr., Ph.D.


Robert F. Powloski, Ph.D.

Since hunger drive is often used as a motivating factor in animal learning experimentation, it was decided to determine the effects of marihuana extract distillate on the eating behavior of rats. Carlini and Kramer (1965) found marihuana extract injections to have a facilitory effect upon maze performance. They suggested that facilitation could have resulted from an increase in hunger drive. However, if the dosage level is high, this effect may last for a short time and be followed by a disinterest in food. Scheckel et al. (1968) report that some monkeys, at very high dosage levels of tetrahydrocannabinol starved to death in post-drug depressions. Human studies indicate some increased hunger or

"taste enhancement" (Grinspoon, 1968; Hollister, et al., 1968; Ames, 1958).

Subjects were 20 male and 20 female adult Sprague-Dawley albino rats, maintained in home cages with ad-lib food and water. Each animal was assigned to one of five groups so that each group contained four males and four females. Each group received one dosage level of the drug throughout the entire experiment. Three dosage levels and two controls were used. Food deprivation levels of ad-lib, 12, 24, and 48 hours were assigned according to a balanced Latin square design. The drug, marihuana extract distillate, was administered through an intraesophageal tube and hypodermic syringe. The study was divided into two parts, each of four weeks' duration. In the first, after administration of the drug, the animals immediately were placed into a cage with a known amount of food present. The food was weighed after three and 24 hours to determine the amount of food eaten. The second experiment of the study repeats all procedures except animals were not given food until 4-hour after the drug was administered.

Results show an inverse relationship between dosage level of marihuana extract distillate and amount of food eaten. Effects of dosage level, hours of deprivation, sex, latency of food presentation, and the possibility of tolerance or increased sensitivity to the drug are discussed.

**THE EFFECTS OF MARIHUANA EXTRACT DISTILLATE
ON EATING BEHAVIOR OF RATS**

**by
TERRIE WETLE**

**A thesis submitted in partial fulfillment of the
requirements for the degree of**

**MASTER OF SCIENCE
in
PSYCHOLOGY**

**Portland State University
1971**

TO THE OFFICE OF GRADUATE STUDIES:

The members of the Committee approve the thesis
of Terrie Wetle presented June 30, 1971.

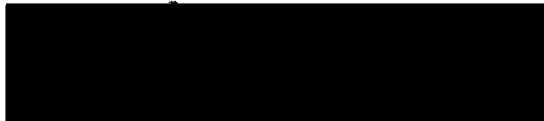

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June 30, 1971

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To a time of waiting I allude

When I offer gratitude,

A year's gestation this did take,

guided by Cord B. Sengstake.

The help from him in kind and size

I could never minimize.

I also thank and will ne're forget

The Jones-Powloski Duet.

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REVIEW OF LITERATURE

Cannabis sativa is indeed a ubiquitous plant, both geographically and historically. The earliest record of use of the drug is found in a Chinese compendium of medicines, the herbal of Emperor Shen Nung, dated 2737 B.C. (Grinspoon, 1969). Its use as an intoxicant spread from China to India, then to North Africa and from there to Europe in about 1800 A.D. Between 1840 and 1900 more than one hundred medical articles were written recommending it for various ailments (Ames, 1958).

In the Western Hemisphere, marihuana had been known for centuries in South and Central America, but was not used in the U. S. as a therapeutic until the 19th century and as an intoxicant in the 1920's (Grinspoon, 1969; Weil et al., 1968).

The medical use of Cannabis sativa was particularly prominent in India; however, in the 19th century, the drug was widely prescribed in the Western world for ailments such as coughing, fatigue, rheumatism, asthma, delirium tremens, migraine headache and painful menstruation. However, its use declined somewhat with the introduction of synthetic hypnotics and analgesics, and its final demise as a medical aide was brought about by the Tax Act of 1937 (Grinspoon, 1969). Federal control of marihuana is presently the responsibility of the Federal Bureau of Narcotics under the Marihuana Tax Act of 1937 (U. S. Code Title 26, Sections 4, 741-4, 776). The act requires all persons with legitimate need to handle marihuana to register and pay an occupational tax,

requires that all marihuana transactions be recorded on official forms provided for that purpose, makes transfers to a registered person subject to a tax of \$1 per ounce and makes transfers to an unregistered person subject to a prohibitive tax of \$100 per ounce.

Marihuana, or hemp is an herbaceous annual growing three to eighteen feet in height depending on soil and climate, with male and female flowers growing on separate plants. When the female plant is about to flower, the tops become covered with a multitude of pluricellular glandulose hairs. The tops are very sticky, and a resin often spreads to the surface of the leaves or branches. This resin appears to contain most of the intoxicating principle of the plant. In the Far East, this resin, charas, is dried, then pressed to produce a greenish-black mass which is then smoked with tobacco. Ganja is a similar resinous mass which is also smoked with tobacco. Bhang is a tea-like beverage or candy produced from the resinous upper leaves of the female plant (Adams, 1940; Ames, 1958). In the U. S. and several other countries, the tops of the flowering plants are cut and dried, the coarse material removed and the remaining leaves chopped to be smoked in either a cigarette or pipe. Charas is the highest grade of Cannabis and is also properly called Hashish, though this name in common usage includes some inferior grades (Grinspoon, 1969).

The use of Cannabis sativa as an intoxicant has taken many forms. The Hindus, in early times, regarded it as a holy plant, believing that the gods extracted nectar from it. Much of the sanctity was due to the

belief that the drug "cleared the head and stimulated the brain to think." Some Mohammedan sects regarded the plant as an embodiment of the spirit of the prophet Khizer Elijah. The lives of some tribes in the Congo center around hemp, and it is smoked regularly. The man who commits a misdeed is condemned to smoke until he loses consciousness. In South Africa, some women smoke in order to stupefy themselves during childbirth, and later the children are given a mash of ground up bread and marihuana when they are weaned. It is also recommended in this area as a local application for snake bite and cancer, similarly for malaria, anthrax and dysentery (Ames, 1958).

As interesting as these reports might be, more information regarding the effects of the drug may be gained from reviewing scientific literature. First, the subjective effects as reported by human subjects will be discussed in relation to both mood and perceptual changes, next the physiological changes are considered, followed by performance test results and finally a review of the studies done with animals.

It is important to note that there are many contradictions concerning the effects of the drug. Often these can be attributed to differences in dosage levels, route of administration, form of Cannabis used, poor experimental design or bias of the experimenter. Especially in the early studies, the experimenters seemed hard pressed to "prove" that the use of Cannabis was followed without exception by a psychosis, leading to increased sexuality, increased criminality and total lack of ambition, and was in most cases a major cause of addiction to heroin

(Abelson, 1968; American Medical Association, 1967; Ames, 1968; Charen et al., 1946; Gaskill, 1945; Keeler, 1967; Keeler, 1968; Nesbitt, 1939; Siler et al., 1933; Sonnenreich et al., 1962; Tylden, 1967; Wolff, 1948). In other studies, physical symptoms are complicated by the transport media for the drug since Marihuana is often administered with other presumably inactive substances. Ames (1958) reports that severe abdominal cramps and diarrhea were direct symptoms, though he later admits that these "may be accounted for in part by the large amount of liquorice contained in the 48 pills given the subject." Many of the studies discussed below suffer from poor design and are included for their historical interest rather than scientific significance. In reviewing the following studies a need for well-designed basic research in marihuana effects becomes apparent.

In the 1940's it was determined that the active constituents of marihuana were various isomers of tetrahydrocannabinol (Grinspoon, 1969). Recent studies have determined that ⁹ tetrahydrocannabinol and ⁸ tetrahydrocannabinol are found in marihuana (Hollister et al., 1968; Lerner, 1963) and have marihuana-like effects in man (Isbell, 1967).

⁹ -tetrahydrocannabinol, both as a natural extract and synthetically produced, has been used in various human and animal studies. Other administration forms are smoking, ingesting natural marihuana and various extracts. Vieria et al. (1967) report that smoking induces more intense intoxication than eating or chewing the drug. However, the symptoms are similar if dosage level of ingestion is increased. Until recently, the

most common form of standardizing the potency of the drug was through the abolition of the corneal reflex of rabbits. A positive assay is the amount of drug needed to abolish 80% of the responses in a three-minute period of measurement (Salustiano et al., 1966). For a more complete description of this technique, see Valle et al. (1966). Potency has been found to correlate closely with the amount of ⁹ tetrahydrocannabinol in the sample (Hollister et al., 1968). In more recent studies, dosage levels are given in terms of ⁹ tetrahydrocannabinol.

Subjective Reports - Mood

A summary of the studies utilizing subjective reports from human subjects is given in Table I. The symptoms described run the gamut from pleasant or beneficial, through confusing and unpleasant to panic. Often many of these different symptoms are described by the same subjects at various levels of intoxication.

A typical course of intoxication is given by Grinspoon (1969).

The intoxication is initiated by a period of anxiety within 10 to 30 minutes after smoking, in which the user develops fears of death and anxieties of a vague nature associated with restlessness and hyperactivity. Within a few minutes he begins to feel more calm and develops definite euphoria; he becomes talkative. . . is elated, exhilarated. . . begins to have. . . an astounding feeling of lightness of the limbs and body. . . laughs uncontrollably and explosively. . . without, at times, the slightest provocation. . . has the impression that his conversation is witty, brilliant. . . The rapid flow of ideas gives the impression of brilliance of thought and observation but confusion appears on trying to remember what was thought. . . he may see visual hallucinations. . . flashes of light or amorphous forms of vivid color which evolve and develop

into geometric figures, shapes, human faces and pictures of great complexity. . .After a longer or shorter time, lasting up to two hours, the smoker becomes drowsy and falls into a dreamless sleep and awakens with no physiologic after-effects and with a clear memory of what happened during the intoxication.

TABLE I

SUBJECTIVE REPORTS - MOOD CHANGES

Mood Change	Study in which it was reported*	
Satisfying, pleasurable	23, 24	
Laughter, happiness	2, 5, 8, 16, 21, 23, 35	
Witty, brilliant	2, 8, 21, 23, 24	
Euphoria, elation	2, 5, 8, 16, 21, 23, 27, 35, 52	
Excitement, hyperactive	2, 8, 16, 35, 41	
Talkative	2, 8, 21, 35	
Lightheaded, dizzy	5, 8, 23, 52	
Increased sexuality	8, 11, 35	No increase 2
Increased objectivity	21	
Increased aggression	7, 35, 41	No increase 23
Confusing, unpleasant	2, 8, 23, 24	
Anxious, panic	2, 7, 8, 11, 21, 23, 35	
Fears, paranoia	2, 8, 21, 35	
Sleepy, dreamy	2, 5, 7, 8, 20, 21, 23, 35, 41, 52	
Relaxed, calm	21, 23, 35	
Depressed	11, 41	
Stupification, unconscious	20, 35	

* Indicates number of study in reference section.

For the most part, most of the symptoms in Table I need no explanation; however, there are a few worth noting. The first of these is a report of increased sexuality. Ames (1958) describes this as a "warm glowing" feeling in the area of the pelvis, and a lowering of inhibitions. One subject, aged 32, who had smoked the drug for many years stated that "dagga (marihuana) means women, murder and fight." He claimed that his sexual vigor was so enhanced that he had slept with four or five women in a single night. However, further investigation revealed that this particular subject was definitely mentally disturbed before using the drug, and his reports about the drug conflicted from one time to the next.

Charen et al. (1946) present reports of increased sexuality but attributes this to lowering of inhibitions and positive group sanctions. Nesbitt (1939) reported enhanced sexual drive but presents no supporting evidence. The Mayor's Committee on Marihuana (Allentuck, 1942) denied any increase in sexual drive due to the drug. Sexual "exaltation" has been reported in only one animal study (Vieria et al, 1961) but there only as a casual observation. Adams (1940) states that although the drug may lower inhibitions, it is definitely not an aphrodesiac.

The most often mentioned symptom in all of the literature, both popular and professional, is euphoria. "The subject first feels himself. . .capable of extraordinary feats of prowess. . .He may suddenly be overcome by absurd and irresistible laughter induced by any trifling incident which is very often not amusing even to the slightest

degree" (Adams, 1940, p. 117). However, experienced subjects are able to control this euphoria to a certain degree if an external task is presented (Weil et al., 1968). Often, this "vivid sense of happiness" is not linked with any particular stimulus but rather just a general sense of well being (Nesbitt, 1939). It is at this stage of the intoxication that the subject feels particularly brilliant and witty and will often become very talkative. Ames (1958) quotes one subject, "There is no mental or physical feat of which I do not feel capable. I am enjoying talking because so many different associations occur to me." p. 980. Another subject reported that he was acquiring deeper insight into basic personality structure and that he had a new awareness of the nature of things. However, this "increased awareness" is not without its problems. To continue the quote, ". . .my talk is disconnected only because I immediately forget previous statements." p. 981. A similar phenomena is reported by one of Weil's et al. (1968) subjects, ". . .there was a sense of the past disappearing as happens when you're driving too long without sleeping. With a start you wake up to realize you were asleep for an instant; you discover yourself driving along the road. It was the same tonight with eating a sandwich. I'd look down to discover I'd just swallowed a bite but I hadn't noticed it at the time (p. 1240)." This "performance without awareness" is reported by another of Weil's subjects, "Time seemed very drawn out. I would keep forgetting what I was doing, especially on the continuous performance test, but somehow every time the 'X' (critical letter) came up, I found myself

pushing the button (p. 1240)."

There are conflicting reports as to whether this sense of prowess and capability lead to hyperactivity. All reports of hyperactivity are found in "lists" of symptoms, either related by habitual users or as "common knowledge." Not one study substantiated this claim with empirical evidence. On the contrary, all reputable studies report, instead, a very relaxed dreamy state in which many actions are "considered" but few undertaken. Weil et al. (1968) reports that while in this state, subjects are able to perform adequately but would much prefer to simply "enjoy" the experience. The same argument holds for reports of increased "aggression." Although this is a popular belief in the folklore of the drug, there is not a single well-designed study to support this supposition. In contrast, Santos et al. (1966) in a well-controlled study demonstrated that marihuana decreased both aggression and spontaneous motor behavior in mice. This has also been demonstrated in primates (Scheckel et al, 1968).

Paranoia, anxiety, fears or panic are another often reported symptom complex. The degree of this fear may be controlled by two factors. The first is dosage level. The most severe fear reaction is reported by Ames (1958) only in patients receiving high dosage levels. One patient believed that simple electrophysiological equipment with which he was familiar was really giving him electroconvulsive shock therapy. The second factor as Adams (1940) suggests, is that the subject may become extremely more sensitive emotionally. A subject who normally

dislikes someone slightly will have an intense hatred under the influence of the drug. In this sense, any vague fear will be magnified into a panic. Therefore, the degree to which the situation is potentially frightful may also be a factor.

This increased fear is reported to alternate with a mood of extreme detachment. Ames (1958) said that subjects could report very painful or unusual symptoms with a totally detached manner as if their body were not their own. Users often report a sensation as if they are merely watching a scene and that they are one of the actors. Scheckler (1968) reports what appears to be a similar reaction in monkeys at higher dosage levels.

Subjective Reports - Perceptual

Perhaps the most common changes reported in the popular literature are those within the sense modalities. They are reported as "enhancement" or "distortion" depending upon the philosophical bent of the researcher. Each sense modality will be discussed in turn, describing both subjective reports and empirical evidence.

TABLE II
SUBJECTIVE REPORTS - PERCEPTUAL CHANGES

Perceptual Change	Study in which it was reported*
Hearing "enhanced"	3, 7, 8, 21, 23, 27, 35
Auditory hallucinations	27
Hallucinations; visions	2, 7, 8, 21, 23, 27, 35
Visual perception distorted	2, 5, 8, 23, 27, 35
Visual perception enhanced	7, 8, 16, 21, 35
Time distortion	5, 3, 8, 16, 21, 23, 27, 35, 52
Spatial distortion	2, 5, 8, 16, 27, 35
Pain diminished	35 Increased 8
Warmth or Cold in extremities	8, 20, 23, 35
Extremities, light, floating	8, 21, 35, 27, 35
Taste enhanced	8, 21, 35, 51
Hunger increased	5, 8, 21, 35, 35, 52
Thirst, dry mouth	5, 8, 21, 23, 27 Increased sal. 8

*Indicates number of study in reference section

One of the earliest widespread uses of marihuana in the United States was by jazz musicians for the purpose of enhancing their musical ability. They reported "increased sensitivity to sound and keener appreciation of rhythm and timing" (Aldrich, 1944). As illustrated in Table II, subjects in many studies report increased hearing acuity. This has been variously described as "a lowering of the sensory threshold especially. . .for acoustical stimuli," "sounds are clearer," or "hearing more acute" (Hollister et al., 1968; Nesbitt, 1939). Auditory hallucinations have been reported (Keeler, 1967) with no substantiation. Aldrich (1944) attempted to determine the effects of a "marihuana-like compound" on musical abilities. The drug used was a pyra-hexyl compound, reported by experienced users to be quite similar to marihuana. Aldrich reports a general decrease in ability as measured by the Seashore Test (Seashore, 1938). Subjects reported that they felt they had improved when, in fact, they had not. It is not within the scope of this paper to discuss the limitations of the Seashore Test; however, it is important to note that on some scales of the test there was actual improvement though it is difficult to interpret Aldrich's results, because of ambiguities in design. In addition, he presented neither individual data nor statistical tests for significance. It would suffice to say that impairment, if any, is slight, and the subject definitely reports an enhancement in the sense of hearing.

There are, however, substantiated reports of changes in visual perception. Both enhancement and hallucinations are reported, often by

the same researcher. Ames (1958) quotes a naive subject, describing his first experience with the drug.

With me the first perceptual change was a change in the colour and outline of objects. Colours became striking and vivid--the curtains were a vivid green, the room looked freshly painted and the figures in the room looked as if they had been cut out of cardboard. There was no third dimension. They were flat with bright colours and sharp outlines, and were seen through a screen of moving dots like a newsprint photograph, with moving dots instead of still ones (pp. 979).

These "hallucinations" appeared with the eyes open or closed and did not appear in all subjects. "Hallucinations" are reported in a number of studies often without definition. Allentuck et al. (1942) describe "pseudo-hallucinations" as "flashes of light and apparitions," Hollister et al. (1968) as "visions on the ceiling" and finally, Adams (1940) as an enactment of their "most intimate and secret thoughts." Grinspoon (1969) emphasizes a heightening of sensitivity to external stimuli, "revealing details that would ordinarily be overlooked, makes colors seem brighter and richer, brings out values in works of art that previously had little or no meaning to the viewer." Again, it is important to note that these effects are somewhat dependent on dosage level. Those studies reporting the most dramatic visual changes were those using very high dosage levels.

Other related changes are of some interest. Ames (1958) reports an increase in both intensity and duration of after-images, though he does not describe this in detail.

Two distortions which appear to be quite interrelated are those of

perception of time and space. Weill et al. (1968), in a carefully controlled study using both naive and experienced subjects, demonstrated a change in judgment of time. Under influence of the drug, many subjects doubled their initial (undrugged) estimate of a 5-minute span. This same observation of an increase in "subjective time" is reported in a number of studies (See Table II). Another often reported symptom is spatial distortion, where distances appear to be longer than they actually are. Ames (1958) links this to the temporal distortions in that subjects felt that a corridor was "immensely long" because it took so long (subjectively) to be wheeled down it.

Data concerning the sense of touch are conflicting. Nesbitt (1939) reports that the sense of pain is diminished but gives no evidence to support this statement. Ames (1958), utilizing the subjective reports of naive subjects, notes an increase in the sensation of pain. One patient reported "agony" from a simple injection, further supporting "enhancement" of external stimuli; however, Ames also points out a "curious detachment" as if it were someone else's body that was experiencing the pain. This "objectivity" is described by a number of subjects in many studies (See Table II).

The final perceptual change to be discussed is that of enhanced taste and smell. Ames (1958) gave the most dramatic report of enhanced taste perception when one of his subjects reported that "even hospital food tastes good." Subjects who were not hungry before would eat with relish when food was presented. Grinspoon (1968) connects this "taste

enhancement" with increased hunger. "It generates a high appreciation of food, so that the person under the influence may approach an ordinary dish with the anticipation of a gourmet confronting a special treat." Hollister et al. (1968) also reports increased hunger for subjects taking tetrahydrocannabinol.

Physiological Changes

Reports of increased hunger lead to a number of interesting physiological studies using human subjects. The first group of studies concerns itself with the level of glucose in the blood, hypothesizing that increased hunger is due to low levels of blood sugar. As can be seen in Table III, three studies report no change in blood sugar level. Eddy (1965) was the only researcher to report hypoglycaemia and gave no empirical support for the symptom. Nausea and vomiting are two other symptoms, possibly related to hunger, that have been reported by a number of researchers. These symptoms are more likely to occur if the user is naive rather than experienced, or if the drug is ingested rather than inhaled, or if the amount used is large rather than small (Ames, 1958; Grinspoon, 1969; Hollister et al., 1968).

TABLE III

PHYSIOLOGICAL CHANGES - HUMAN

Physiological Change	Study in which it was reported.*
Hypoglycemia	16
Plasma glucose, no change	8, 23, 51
Nausea, vomiting	5, 8, 20, 21, 35
Diarrhea	5 **
Diuretic	8, 21, 35
Shaking, trembling	8, 20, 21, 23, 35
Muscular contractions	8
Chest constrictions	23, 35
Shortness of breath	23
Pupil dilation	5, 20
No pupil change	21, 23, 26, 52
Heavy eyelids	11, 22
Conjunctiva injected	5, 8, 23, 26, 27, 52
Headache	2, 8, 20, 23
Electroencephlograph change	8
Ataxia	5, 7, 20, 21, 23, 52

*Indicates number of study in reference section

** See explanation in text

Diarrhea was reported to be caused by marihuana by one researcher (Ames, 1958). However, as previously mentioned this subject was given 48 grains of marihuana, each grain encapsulated in liquorice. Even Ames was forced to admit that the symptoms "may be accounted for in part by the large amount of liquorice contained in the 48 pills." Several studies have indicated that the drug acts as a diuretic, increasing urination in both frequency and amount (See Table III). Increased salivation has also been noted by some (Ames, 1958).

Another group of symptoms include muscular contractions, constrictions of the chest, shaking, trembling and ataxia. As can be seen in Table III those most often listed are shaking and/or trembling. This is usually a result of high doses (Ames, 1958; Grinspoon, 1969). Hollister et al. (1968) reports weakness as demonstrated with the finger ergograph. Hollister stresses the fact that any tremor, if present at all, is very weak, much weaker than that produced by others of the psychoactive drugs. Ataxia, perhaps related to dizziness, is a commonly reported symptom and may be also listed as poor coordination. Muscular contractions were reported by Ames (1958) at high dosage levels. Constrictions or "tightness in the chest" were also listed as symptoms and may also be connected with shortness of breath reported by Hollister et al. (1968).

Various changes of the eye are reported to take place. Two researchers (Allentuck et al., 1942; Gaskill, 1945) support the popular belief that the drug causes dilation of pupils; however, no recent study supports a change in pupil size. The pupil dilation myth may be an

artifact of the practice of smoking marihuana in a darkened room (Grinspoon, 1969). The heavy eyelids reported by two researchers (Charen et al., 1946; Halpern, 1944) may be a result of drowsiness or of muscular weakness (Sengstake, personal communication). The final eye symptom, injection (redness) of the conjunctivae, is a common symptom reported by many researchers (See Table III). Hollister et al. (1968) report that the conjunctivae became injected after the first hour or two and persisted throughout the course of the drug action. This symptom appeared at all dosage levels to some degree.

A final, somewhat "subjective" physiological symptom is that of headache. Although not severe, this is an often reported symptom, especially early in the intoxication (See Table III).

Ames (1958) reports some electroencephlographic changes, though all readings remained within normal limits.

The final category of physiological symptoms to be considered are those dealing with changes in pulse rate and blood pressure. An increase in the rate at which the heart is beating is the most often reported physiological symptom (See Table III), and often there is considerable tachycardia. Gaskill (1945) is the only researcher to report a decrease in heart rate, which reportedly occurs when the patient "loses consciousness." From Major Gaskill's description, it is more likely that his subject went to sleep. Ames (1958) and Grinspoon (1969) tentatively report a rise in blood pressure. However, Hollister et al. (1968) in a well controlled study demonstrated a decrease in blood pressure. Both increase and

decrease are well within normal limits and may be artifacts of the experimental situation.

Performance Tests - Human

Of final interest in human studies before reviewing work done with animals are those studies which give some measure of performance under the influence of the drug.

Previously mentioned is Aldrich's (1944) study to test the effects of marihuana on musical ability, in which he found some decrease in ability as measured by the Seashore Test (1938). However, Morrow (1944) reports no impairment in hearing acuity or musical ability. Morrow also reports no change in the ability to judge short periods of time or short distances though the drug did affect reaction time to complex stimuli. Florence Halpern (1944) used intelligence tests in examining the effects of marihuana. Performance on number concepts tended to decline, but scores on tests of memory or verbal facility either remained unchanged or improved. Allentuck et al. (1942) also noted that scores on achievement tests were only "slightly lowered, if at all." Hollister et al. (1968) noted a slowing of performance on a Number Facility Test, though the accuracy remained high in his group of subjects who were "well educated." He also noted an impairment in accuracy in the Flexibility of Closure Test.

Weil et al. (1968) used a number of performance tests in a well controlled study using both naive and experienced subjects, placebos and marihuana. Experienced users knew that they were smoking marihuana.

Attempts were made to control dosage by instructing the subjects in a standard technique to use in smoking their two cigarettes. They found no change in either the naive or experienced group in a Continuous Performance Test in which the subject was to respond to a target letter whenever it was flashed on a screen. Performance on a digit symbol test was impaired in the naive user, but not with experienced users even at the highest dosage levels. The same sort of data was obtained for pursuit rotor performance. In this case, however, experienced subjects actually improved, perhaps from practice effect. Perhaps the most important differences are those between the experienced and naive subjects. All of the experienced users felt "high" but showed little impairment, while only one naive subject felt "high" and yet all naive subjects showed some degree of impairment. This indicates that experienced users are able to compensate for drug effects, to some degree. These results also lend support to the hypothesis that new users must "learn" to feel "high" by learning to recognize the symptoms of "intoxication."

Animal Studies

As can be seen in Table IV, relatively few studies have used animals as subjects, in part because of difficulties in administering controlled doses of the drug. Five studies used a marijuana extract (Carlini & Carlini, 1965; Carlini & Kramer, 1965; Persaud et al., 1967; Salustiano et al., 1966; Santos et al., 1966), five used tetrahydrocannabinol (THC) (Dagirmanjian et al., 1962; Garriott et al., 1967; Lapa et al., 1968;

Schackel et al., 1968), one used both an extract and THC (Irwin, unpublished), one used hashish smoke extract (Vieira et al., 1967), and one Brazilian researcher used "combustion products of marihuana" (Vieira et al., 1961). However, only an abstract of this study was available.

TABLE IV

BEHAVIORAL AND PHYSIOLOGICAL CHANGES - ANIMAL

Change	Study in which it was reported*					
	Mice	Monkey	Cat	Rat	Dogs	Rabbit "Animals"
Ataxis	25, 51	25	25		41	
Tremors	51	42				21
Abdominal contractions	50					
"Postural arrest"	25	25,42	25			
Motor activity-increase				10		
Motor activity-decrease	25, 41					
Motor activity-no change	40, 41					
"Excitation"	50, 51			25		
Paralysis, depression	50	42				
Agression-increase	50			10		
Agression-decrease	19, 40 41					
Vocalization increase				10		
Corneal reflex decrease					40,41 48	

TABLE IV - Continued

BEHAVIORAL AND PHYSIOLOGICAL CHANGES - ANIMAL

Change	Study in which it was reported*					
	Mice	Monkey	Cat	Rat	Dogs	Rabbit "Animals"
Narrowing palpebral fissure	50	50		50		
Hunger increase				10		
Hunger decrease		42		10		
Vomiting, diarrhea						21
Sexual "exaltation"	51					
Increased DNA in brain				9		
Blood pressure decrease	14		14			
Respiration decrease	14	25	14			
Stunting of fetus	36					

*Indicates number of study in reference section.

An important group of effects deal with muscular contractions and motor activity. Ataxia has been reported in dogs (Santos et al., 1966), mice, monkeys and cats (Irwin, unpublished manuscript). Grinspoon (1968) reports that animals exhibit "tremors" at high dosage levels, and this is supported by evidence from a study with monkeys recently completed by Scheckel et al. (1968). Abdominal contractions, similar to parturition, were observed in mice (Vieira, 1967). Perhaps the most dramatic symptom is the tendency of an animal to hold a particular position for a long period of time. Irwin (unpublished manuscript) calls this "postural arrest." He observed this in mice and squirrel monkeys. Scheckel et al. (1968) describe a similar symptom in his study, also with monkeys. Possibly related to postural arrest is a decrease in spontaneous motor activity also reported by Irwin (unpublished manuscript), though slight. Santos et al. (1966) report decreases in spontaneous motor activity in mice only at very high dosage levels (lethal to some mice). At lower levels he found no change in motor activity, results supported by a similar mouse study Hoshino et al. (1966). Carlini et al. (1965) working with rats reports an increase in motor activity; however, they related this to increased excitability, as supported by Vieira (1967), whose mice were particularly susceptible to auditory stimulation. Scheckel et al. (1968) reports that, with monkeys, a "stimulant phase" in which the animals appear to be hallucinating is followed by a "depression" in which the monkey crouches motionless for periods up to a week, sometimes dying of starvation. Vieira (1967) reports a similar

depression with mice, which often led to paralysis and death at high doses (350 mg/kg of hashish smoke extract). Vieira (unpublished manuscript) also reports that marihuana increases "excitability." In the state of chronic intoxication, the animals lose their natural charm and vivacity, taking on a morbid aspect. . . sexual exaltation and aggressiveness were observed." It should be noted that these dosage levels, if accurate, are ridiculously high.

Changes in aggression have been a "folklore" symptom of marihuana for some time. Carlini and Kramer (1965) report increased aggression as a side observation in a learning study with rats. A number of well-controlled studies with mice report decreases in aggressive behavior, even in strains of mice bred for fighting behaviors (Garriott et al., 1967; Salustiana et al., 1966; Santos et al., 1966).

Carlini and Kramer (1966) report increased vocalization whenever their rats were touched. This may be a fear reaction, as reported in the human studies discussed previously.

A narrowing of the palpebral fissure has been noted in some animals, particularly mice (Vieira, 1967), and perhaps corresponds to "heavy eyelids" reported by human subjects (See Table III).

The drug appears to have a complex effect on hunger related to the dosage level. Carlini and Kramer (1965) report increased hunger as a result of injection of marihuana extract. However, if the dosage level is high, this effect lasts for a short time and is replaced by a disinterest in food. Scheckel et al. (1968) report that some monkeys (at very high

dosage levels) starved to death in their post-drug depression. Grinspoon (1969) reports diarrhea and vomiting in some animals at very high dosage levels.

Dagirmanjian et al. (1962) report decreases in blood pressure and respiration in both mice and cats at high dosage levels of tetrahydrocannabinol.

Only two studies dealt with the effects of marihuana on learning. In one, Vieira et al. (1967) demonstrate specific suppression of the Conditioned Avoidance Response, using a Warner-type shuttle-box. The dosage levels here were extremely high, 250 mg/kg hashish smoke extract, lethal to many mice.

The second study is of particular interest. Carlini and Kramer (1965) used a Lashley III alley maze to test the effects of marihuana extract on running time and number of errors. They found that animals injected with the extract before running, group II, performed significantly better ($p < 0.05$) than the control group. However, rats receiving marihuana injections after running, group III, showed more errors than even the controls, who were injected with a control solution after the trial. There are a number of weaknesses in this study. From the design, there was no control group receiving injections before trials; therefore, it is possible that an injection of the control solution before the trials could have had an effect similar to the marihuana extract. The study appears to have been designed in this manner in an attempt to determine effects of marihuana on memory consolidation. It appears from the data

that the group distributions were very skewed (i.e., a mean of 187.9 seconds, running time, with a standard deviation of 236). However, assuming for a moment that injections of marihuana extract do improve maze performance, we can hypothesize a number of explanations. First, we might hypothesize that the improvement is a result of increased hunger. Increased hunger has been shown to improve running speed (Kintsch, 1962; Reynolds et al., 1960; Zaretsky et al., 1966). The proposal that marihuana might increase hunger is in concordance with previously mentioned reports of human subjects (Allentuck, 1955; Grinspoon, 1969; Hollister et al., 1968; Siler et al., 1933; Veiga et al., 1962; Weil et al., 1968). However, Carlini and Kramer (1965) are the only researchers to report increased hunger in animals. At dosage levels higher than 30 mg of marihuana extract (a high dose), eating behavior was suppressed. Although these researchers go into a detailed description of why injections after the trials do not enhance learning, they offer no hypothesis as to why they might enhance learning when injected prior to the trials.

A second hypothesis might relate to either a change in perceptual abilities or an enhancement in learning processes. Human studies, as previously cited, give some support to the idea of changes in perception. However, if any real conclusions are to be drawn from animal studies, it is first necessary to determine the effects of the drug on eating behavior, since food is, by far, the most common reinforcer.

It is the purpose of this study to determine the effects of marihuana, at different dosage levels and deprivation states, on eating behavior in rats.

CHAPTER II

METHOD

Marihuana extract distillate, MED, obtained from the National Institute of Mental Health, Chevy Chase, Maryland, was used in an effort to control the amount of tetrahydrocannabinol, Δ^9 THC. The distillate also contains Δ^8 THC and other, possibly active, chemicals. The dosage levels were chosen in consideration of a number of factors. A 300 mg Mexican marihuana cigarette has been calculated to contain 1.5% THC from which about 50% is absorbed by the smoker (Efron, 1967). Isbell (et al, 1967) reports that marihuana is about three times as potent when smoked as when taken orally. Accordingly, comparable doses per 70 kg man per cigarette can be expected to be about 0.052 mg/kg smoking or 0.155 mg/kg orally. Carlini and Kramer (1965) used a dosage level of 10 mg/kg marihuana extract, THC content unknown. Therefore, dosage levels were chosen such that the lowest, 0.15 mg/kg corresponds to the amount which causes perceptual changes in man. The medium dosage level is ten times greater and corresponds to a "heavy" dose in man and the high dosage level is ten times greater than that. (Isbell et al, 1967)

The drug solutions were prepared in the following manner. The marihuana extract distillate, containing 17.1% Δ^9 THC, was suspended in a normal saline solution with 4% Tween-80 to aid suspension (Carlini and Kramer, 1965). The drug was administered orally, with an intraesophageal

tube and an hypodermic syringe.

Subjects were 20 male and 20 female Sprague-Dawley albino rats. They were maintained in their home cages on ad-lib food and water during the course of the experiment. Each of the animals was assigned to one of five groups, so that each group contained four males and four females. The first group (THC) was given marihuana extract distillate at the level of 15 mg/kg body weight; the second group (THC), 1.5 mg/kg; the third group (THC), 0.15 mg/kg. The fourth group, TWN, received only the carrier solution and the fifth group, MOCK, underwent the same administrative procedure but with no actual ingestion of any substance.

Each animal was tested once under each of the following four conditions; food and water present at all times (ad-lib); food withdrawn 12 hours prior to ingestion of drug, water present at all times (12 hour); food withdrawn 24 hours prior to ingestion of drug, water present at all times (24 hour); food withdrawn 48 hours prior to ingestion of drug, water present at all times (48 hours). Each animal was tested under all four deprivation conditions with approximately one week rest after each test. The order of presentation of the four deprivation schedules was assigned according to a balanced Latin square design.

The study was divided into two parts, each of four weeks' duration. In the first part (Experiment I), after administration of the drug, the animals were immediately placed into a cage with a known amount of food present. The food was weighed after three hours and again after 24 to determine the amount of food eaten during each of these periods.

Experiment II repeated all procedures unchanged except that the animals were not given food until $\frac{1}{2}$ -hour after the drug was administered. This was to allow for drug effects to appear before eating began.

CHAPTER III

RESULTS

Data for males and females were examined separately using Cochran and Cox's (1957) design to determine residual effects. Finding none to be significant, the data were collapsed over order yielding four animals per cell for Winer's (1962) p*q factorial design for repeated measures. The results of that analysis are presented in Table V.

TABLE V

F VALUES FOR ANALYSIS OF VARIANCE

Part 1

No Latency

Sex		F Values
Male	Dosage Level	Deprivation Level
0-3 hr	0.30	26.76**
3-24	18.49**	1.34
0-24	23.58**	17.51**
Female		
0.3 hr	4.25*	20.10**
3-24	4.92**	1.73
0-24	9.67**	17.31**

TABLE V - Continued

Part 2

 $\frac{1}{2}$ -Hour Latency

Sex		F Values
Male	Dosage Level	Deprivation Level
$\frac{1}{2}$ -3 hr	3.14*	37.08**
3-24	10.34**	0.51
$\frac{1}{2}$ -24	24.39**	38.18**
Female		
$\frac{1}{2}$ -3 hr	9.70**	22.04**
3-24	1.63	3.25*
$\frac{1}{2}$ -24	6.32**	18.89**

* = $p < 0.05$ ** = $p < 0.01$

In initial examination of that table, it can be observed that deprivation level is a significant factor in determining the amount of food eaten. In addition, level of deprivation appears to be most important during the first three hours of food presentation. A Newman-Keuls operation (Winer, 1962) was performed to determine the direction of effects. The results are presented in Table VI.

TABLE VI
NEWMAN-KEULS RESULTS

Part 1

No Latency

Sex	Ordered Means							
Male	Dosage Level				Deprivation Level			
0-3 hr	F not significant				Ad	12	48	24
3-24	THC ₁	THC ₂	MOCK	THC ₃	TWN	F not significant		
0-24	THC ₁	THC ₂	MOCK	THC ₃	TWN	Ad	12	48 24
Female								
0-3	THC ₁	THC ₂	THC ₃	TWN	MOCK	Ad	12	48 24
3-24	THC ₁	THC ₂	MOCK	TWN	THC ₃	F not significant		
0-24	THC ₁	THC ₂	MOCK	THC ₃	TWN	Ad	12	48 24

Part 2
 $\frac{1}{2}$ Hour Latency

Male	Dosage Level					Deprivation Level		
$\frac{1}{4}$ -3 hr	THC ₁	THC ₂	THC ₃	MOCK	TWN	Ad	12	48 24
3-24	THC ₁	THC ₂	THC ₃	MOCK	TWN	F not significant		
$\frac{1}{4}$ -24	THC ₁	THC ₂	THC ₃	MOCK	TWN	Ad	48	12 24
Female								
$\frac{1}{4}$ -3	THC ₁	THC ₂	THC ₃	TWN	MOCK	Ad	48	12 24
3-24	F not significant					Ad	48	24 12
$\frac{1}{4}$ -24	THC ₁	THC ₂	TWN	THC ₃	MOCK	Ad	48	12 24

underlining indicates that numbers do not differ significantly

THC₁ = 15 mg THC/kg body weight
 THC₂ = 1.5 mg THC/kg
 THC₃ = 0.15 mg THC/kg
 TWN = carrier solution only
 MOCK = procedure, no ingestion

As might be expected, the ad-lib group consistently ate the least amount of food. Similarly, the group deprived for 24 hours ate the most, with the 12 and 48 hour groups falling between.

Of primary interest in this study, dosage level was also a significant factor for both male and female animals. Results of the statistical analysis are presented in Table V. In all cases, dosage level was a significant factor ($p < 0.01$) in determining the amount of food eaten at the 24-hour weighing. However, it can be observed that females were effected somewhat differently than males. In Experiment I, with food presentation immediately following drug administration, females showed drug effects during the first three hours while males did not. Likewise, in Experiment II, with a $\frac{1}{2}$ -hour latency between drug administration and food presentation, while both males and females showed drug effects during the first 3 hours of the experimental period, only the males demonstrated any effects in the 3-24 hour period.

A Newman-Keuls operation (Winer, 1962) was performed to determine the direction of effects and the results are presented in Table VI. In all cases, if \underline{F} is significant, dosage level of Marijuana Extract Distillate is inversely related to the amount of food eaten. The highest dosage level, 15 mg/kg, always resulted in the least amount eaten, the second dosage level group, 1.5 mg/kg, eating somewhat more. No definite trend could be determined for the lowest dosage level or the two controls. In general, similar amounts of food were eaten by these three groups.

No significant interaction was observed between dosage and deprivation level.

Casual Observations

A number of additional observations may be of interest though they were casual. The behavior of the animals at the highest dosage level was quite obviously effected by the drug. The animals would spend long periods of time motionless in their cages, often in unusual positions, i.e., head and one leg raised, standing on hind legs, etc. This is similar to Irwin's (unpublished manuscript) description of "postural arrest." Any sharp noise or movement would cause the animal to change position. Increased vocalization was also noted. Squealing could be elicited by moving an object into the animal's lateral vision. As the study progressed, some animals, at the highest dosage, would exhibit increased vocalization, long after other drug effects had ceased.

If the animal were picked up, urination and defecation usually accompanied the squealing. If the animal were placed on a table or floor, it would spread its legs wide as if for better balance, and either refuse to move or would walk in circles with one foot stationary. If the animal were held suspended, it would hold onto any object, pencils or fingers, which touched its feet. When placed with an estrus female, a male at the highest dosage level showed no interest, his only response being to squeal if touched. A number of times one male stood motionless under his water bottle while the entire contents dripped over him.

Animals at the medium dosage levels rarely exhibited any of the above behaviors. No unusual behavior was observed in either the lowest dosage group or the two control groups.

CHAPTER IV

DISCUSSION

Statements concerning direct effects as examined by this design, although seemingly simple, lead into increasingly complex discussions of the effects of the various independent variables. Two initial observations appear to be; a) that the data indicate that the level of food deprivation has a direct effect on the amount of food eaten, and b) that Marihuana Extract Distillate has a direct effect upon the amount of food eaten, that effect generally being an inverse relation between amount eaten and dosage level of the drug.

The effects of food deprivation were in the direction that would be expected from a number of studies (Dufort et al., 1962; Reynolds et al., 1960). That is, animals tend to eat more with increasing periods of deprivation to a point, after which consumption decreases. Thus, as the animals in this study were deprived for increasing periods of time up to and including 24 hours, they tended to eat more after which (48 hours of deprivation) they tended to eat less. This finding, though not new, points to a consideration that must be made in any experimentation which utilizes deprivation in an effort to increase motivation.

Of more interest to this investigator were effects related to dosage level. At first glance, it appears that evidence indicating decreased eating behavior is in direct opposition to other studies relying

on human reports (Ames, 1958; Grinspoon, 1968; Hollister et al, 1968). However, both Ames and Grinspoon relate "increased hunger" to "taste enhancement." Thus, a person eats more because the food tastes better rather than because of increased hunger. "Taste enhancement," if present in rats, may have little effect of the taste of lab chow, the food eaten by the experimental animals. If some other more "desirable" food were offered, this effect might be observed.

Carlini and Kramer (1965) reported "increased appetite." The animals reportedly exhibited this increased appetite for about "3 to 5 minutes". However, as time elapsed, the animals showed "signs of depression and did not look for food any more (pp. 177)." The data in the present study may be interpreted to support Carlini and Kramer's observation. Since the animals in Experiment I were presented food with no delay, they may have exhibited an initial burst of eating behavior followed by a depression of eating. However, the design of the study did not allow for direct observation of this effect since the food was weighed only at 3 and 24 hour periods. The observation that the animals in Experiment II ate less food than those in Experiment I when compared to their respective controls offers indirect support to an "initial increased hunger" hypothesis. Thus, by delaying presentation of food in Experiment II until after the "initial appetite" would have occurred, the total amount of food eaten in the 3-hour period is decreased considerably.

Another interpretation of these same data is possible. Assuming for

a moment that no initial "increased appetite" occurs as a result of the drug ingestion, we still expect animals to eat when presented with food, particularly those which had been deprived for periods up to 48 hours. In Experiment I (no delay) the animals would have been able to do a good deal of eating before drug effects appeared. However, in Experiment II ($\frac{1}{2}$ hour delay) the effects of the drug have appeared before food is presented, resulting in less being eaten. Further research is necessary to determine the exact course of drug effects.

The actual depression of eating behavior may be a function of decreased hunger, or a function of a general decrease in motor activity.

Also of interest is the observation that females appear to be effected somewhat differently by the drug than males. Again, more than one interpretation is possible. Because the females were approximately 150 grams lighter than the males, and because dosage was determined in mg/kg, it is possible that effect of dosage level is not described by a linear model. In other words, a 10 mg dose to a 200 mg animal may not be comparable to a 20 mg dose to a 400 mg animal. It is also possible that females were either more susceptible to drug effects, or that they reacted more quickly at those dosage levels. This same phenomenon has been observed with other drugs (Irwin, personal communication). In the first portion of the study when food was presented directly after drug administration, dosage level was significant only for the females during the first 3-hour period. In the second portion of the study, when a

latency period of $\frac{1}{2}$ hour occurred between drug administration and food presentation, females again showed a higher level of significance ($p < 0.01$) than did the males ($p < 0.05$). The observation that females showed no drug effect in the 3-24 hour period lends some support to the hypothesis that females may react and recover more quickly from the drug effects.

Finally, the casual observations give some indications that the effects of the drug are not confined to a general suppression of movement. "Enhancement" of perceptual experience could be a possible explanation for the increased vocalization, urination and defecation occurring when an animal was disturbed. Of further interest is the observation that some behavioral changes appeared to outlast the "direct effects" of the drug. Whether this may be due to "long term effects" or to learned responses is beyond the scope of this study. However, fertile ground for further research is suggested.

CHAPTER V

CONCLUSIONS

This study has shown that Marihuana Extract Distillate depresses eating behavior in rats at medium and high dosage levels. This may be due to decreased appetite, or by a general decrease in physical activity. There is also some indication that females may be effected by the drug somewhat differently than males. Further research is necessary to determine the basis of that difference.

Whatever the explanations for these effects, they lead to considerations which must be made in any research utilizing marihuana as an independent variable and food or food deprivation as a motivating factor.

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